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Award Number: W81XWH-10-1-0772

TITLE: Characterizing and Targeting Androgen Receptor Pathway-Independent Prostate Cancer

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REPORT DATE: September 2011

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release; distribution unlimited

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| REPORT DOCUMENTATION PAGE | | | | Form Approved OMB No. 0704-0188 | |
|---|------------------|--------------------------|----------------------------|--|---|
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| 1. REPORT DATE (DD-MM-YYYY) 01-09-2011 | | 2. REPORT TYPE Annual | | 3. DATES COVERED (From - To) 1 SEP 2010 - 31 AUG 2011 | |
| 4. TITLE AND SUBTITLE Characterizing and Targeting Androgen Receptor Pathway-Independent Prostate Cancer | | | | 5a. CONTRACT NUMBER | |
| | | | | 5b. GRANT NUMBER W81XWH-10-1-0772 | |
| | | | | 5c. PROGRAM ELEMENT NUMBER | |
| 6. AUTHOR(S) Dr. Phillip Febbo E-Mail: phillip.febbo@ucsf.edu | | | | 5d. PROJECT NUMBER | |
| | | | | 5e. TASK NUMBER | |
| | | | | 5f. WORK UNIT NUMBER | |
| 7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of California San Francisco, CA 94103 | | | | 8. PERFORMING ORGANIZATION REPORT NUMBER | |
| 9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012 | | | | 10. SPONSOR/MONITOR'S ACRONYM(S) | |
| | | | | 11. SPONSOR/MONITOR'S REPORT NUMBER(S) | |
| 12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited | | | | | |
| 13. SUPPLEMENTARY NOTES | | | | | |
| 14. ABSTRACT In this proposal, we aim to test the hypothesis that complete AR pathway inhibition selects for subpopulations of tumor cells that are completely independent of AR signaling and further, that these resistant cells will have activated---and be dependent upon---a limited set of specific survival and growth regulatory pathways (stemming from genomic alterations in specific oncogene networks) that can be identified and targeted. We propose three aims to test our hypotheses. Aim 1 will define the genomic alterations and transcript variants that comprise 'states' of ARIPC. Aim 2 will determine if targeting/inhibiting the survival pathway(s) that emerge following AR pathway ablation will restrain tumor growth. Aim 3 will determine if simultaneously co-targeting the AR pathway and ARIPC survival pathway(s) in AR-sensitive prostate cancers will augment tumor responses and delay/prevent recurrences. During this funding period we have: (i) completed laser capture microdissection of CRPC prostate cancers to acquire RNA and DNA; (ii) completed transcript profiling for 150 CRPC metastasis; (iii) completed genomic analyses for 150 prostate cancer metastasis; (iv) identified a program of AR-repressed genes that may influence the development of CRPC; (v) initiated preclinical studies of two putative AR-bypass pathways. Initiated an integrated molecular analyses of advanced metastatic CPRC to identify additional molecular pathways that operate to promote prostate cancer growth in the absence of AR signaling. | | | | | |
| 15. SUBJECT TERMS prostate cancer, androgens, androgen receptor, molecular profiles | | | | | |
| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERSON |
| a. REPORT U | b. ABSTRACT U | c. THIS PAGE U | | | USAMRMC |
| | | | UU | 13 | 19b. TELEPHONE NUMBER (include area code) |

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Introduction

Studies conducted in the Nelson and Febbo labs involving castration-resistant prostate cancer (CRPC) indicate that although most CRPC tumors exhibit androgen receptor (AR) activity, there is significant heterogeneity in the level of AR activity; some cancers appear to have trivial or no AR activity (“AR-null”) while others have levels of AR activity equivalent to untreated, localized prostate cancer tumors. Of importance, even in tumors that demonstrate global continued AR activity, there are infrequent tumor deposits with no AR expression. Thus, as more potent blockade of the androgen axis is achieved, it is likely that resistant clones/tumors exhibiting an “AR-null” signature will emerge and a greater percentage of patients will have AR-null CRPC. At this time, it is unclear what phenotypes, genotypes, and attendant dominant growth and survival pathways will be operative in an AR-null state.

The objective of this proposal is to test the *hypothesis* that complete AR pathway inhibition selects for subpopulations of tumor cells that are completely independent of AR signaling and further, that these resistant cells will have activated---and be dependent upon---a limited set of specific survival and growth regulatory pathways (stemming from genomic alterations in specific oncogene networks) that can be identified and targeted. This proposal comprises 3 Specific Aims to test our hypotheses. Aim 1 will define the genomic alterations and transcript variants that comprise ‘states’ of ARIPC. Aim 2 will determine if targeting/inhibiting the survival pathway(s) that emerge following AR pathway ablation will restrain tumor growth. Aim 3 will determine if simultaneously co-targeting the AR pathway and ARIPC survival pathway(s) in *AR sensitive prostate cancers* will augment tumor responses and delay/prevent recurrences.

Body

This is a “synergy” project between the laboratories of Dr. Phil Febbo at the University of California, San Francisco (UCSF) and Dr. Peter Nelson in the Division of Human Biology at the Fred Hutchinson Cancer Research Center (FHCRC). Because these are separate awards to the two investigators, this progress report is specific to tasks from the statement of work (SOW) assigned to the Febbo Lab only (or to progress within the Febbo Lab for joint tasks). We have coordinated our submissions and refer to each other’s section when appropriate. As per the instructions, progress is reported in association with each of the relevant tasks listed in the SOW. To complete the project Aims, we have divided the proposed studies into discrete Tasks number Task 1 through Task 5 and are listed as N for Nelson lab, F for Febbo lab, and NF for Nelson and Febbo joint task. The time frame for the Task is noted as Year (Y1-3) and Quarter (Q1-4). Progress:

Task 1. Animal Protocol Administration – This task was originally assigned to the Nelson laboratory where the animal work will be performed. This will be reported on in the Annual Report from the Nelson Laboratory.

Task 2. Analysis of scientific aim 1: Integration of genome-scale bioinformatics-based approaches with quantitative assessments of gene expression measurements to define the pathways associated with ARIPC – This is a shared Task by the Nelson and Febbo laboratories. Both laboratories have made considerable progress and our objective of analyzing 150 CRPC specimens has been exceeded. To date, the Nelson Laboratory has analyzed 150 CRPC specimens through their analysis of samples collected through their warm autopsy series. The Febbo Laboratory has analyzed 54 biopsies of metastatic, CRPC obtained prospectively using CT-guided biopsies of men participating in a clinical trial. In addition, the Febbo laboratory has collaborated with Dr. Terry Furey to perform integrative analysis of RNA and DNA expression data from 156 prostate cancer tumors for which data became publicly available during the first year of this award (Taylor et al. Integrative genomic profiling of human prostate cancer. Cancer Cell. 2010;18(1):11-22) [1]. As such, our analysis to date represents the integrative analysis of 360 prostate cancer specimens of which 223 represent metastatic prostate cancer.

2a. Laser Capture Microdissection of 150 CRPC specimens (Y1Q3)—NF

A significant challenge to understanding the biology of CRPC and identifying pathways associated with resistance is obtaining metastatic samples. Dr. Nelson and his colleagues at the University of Washington have addressed this challenge by supporting a rapid autopsy program over the past 15 years and collecting multiple specimens from men shortly after they have passed away from complications of prostate cancer. The Febbo laboratory has worked to develop techniques facilitating the collection of specimens from patients being actively treated for prostate cancer using radiologically-guided biopsies of metastatic samples. Given the predilection of prostate cancer to metastasize to the bone, obtaining evaluable material with a radiologically guided biopsy is challenging. We have established the methodologies and techniques required for this through support from clinical trials and prior DOD awards (including a DOD Physician Research Training Award).

Our methods are diagrammed in **Figure 1 (next page)**. Including: 1) assessment of the biopsy material by Pathology to determine if prostate cancer is present, 2) collection of prostate cancer cells using laser capture micro dissection, 3) isolation of RNA and assessment of RNA quality using a Agilent BioAnalyzer and quantity using a RiboGreen RNA quantification assay, 4) processing of RNA for hybridization to Affymetrix microarrays, 5) Assessment of microarray quality, and, finally, 6) application of the AR signature to determine relative AR activity level as described in our proposal. After consenting 57 men

on the protocol through which biopsies were performed, 55 patients had biopsies; of the 55 who had biopsies, 33 (60%) were successful. The most common cause for technical failure was a lack of detectable cancer in the biopsy (n=10, 18%) followed by poor microarray quality (n=7, 13%), and finally poor quality RNA (n=4, 7%) (**Fig 1B**).

The overall goal of processing specimens is to assess the levels of AR activity and to subsequently

perform integrative analysis to find pathways associated with low levels of AR activity (i.e. those tumors that are AR-independent). See below (Task 2f for results from these

specimens). These biopsies are currently at Duke and will be transferred to UCSF during this next year so that DNA-based analysis can be completed to facilitate integrative analysis. Once DNA-based analysis is performed, these biopsies will contribute to the total number of samples available for integrative analysis using both RNA and DNA-based data to identify pathways associated with samples having low levels of AR activity.

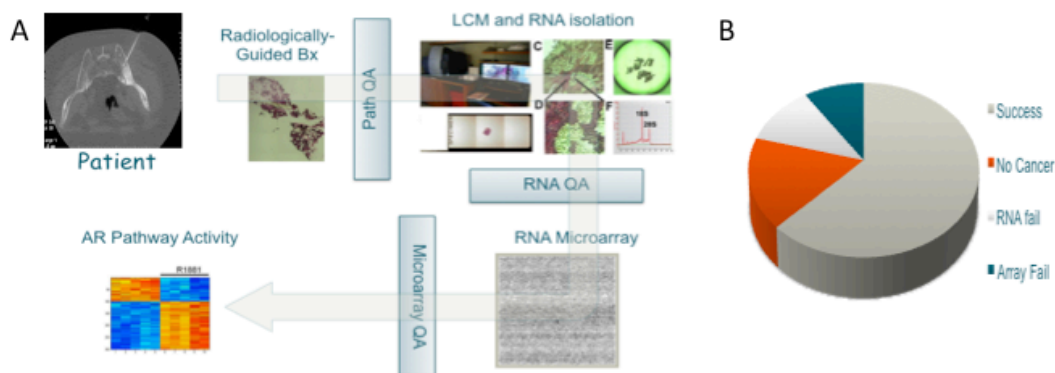


Figure 1: CT-Guided Biopsy Analysis of CRPC. A) Flow diagram of assessment of radiologically-guided biopsies collected from men with CRPC. B) Technical results from prospectively collected mCRPC biopsies (n=54).

2b. (Revised) Splice variant analysis of 150 CRPC specimens (Y1Q4)—F

We have primarily focused on global RNA expression and AR activity from the metastatic CRPC specimens and have not annotated specimens for RNA splice variants at this time. Based upon emerging data from Dr. Stephen Plymate's laboratory and others, splice variants tend to be present in a large number of CRPC tumors but, with few exceptions, the frequency of the splice variants tend to be much less than the full length AR. As the primary mechanism of action of AR splice variations are to maintain AR activity, we have decided to focus on annotating samples for AR activity with the idea that those with high AR activity may be due to splice variation or other mechanisms while those with relatively low AR activity.

2c. (Revised) SNP analysis of 150 CRPC specimens (Y1Q4)-N

This analysis was performed by the Nelson Laboratory.

Milestone #3: Complete processing of 150 CRPC specimens (Y1Q4)

Given the combined activity at the Nelson Laboratories and the Febbo Laboratories, this task has been completed. As mentioned above, we have analyzed a total of 360 prostate cancer specimens for AR activity, expression, and DNA-copy number changes. Given our use of publicly available data, we have focused on this analysis and less on deriving AR splice variation. We anticipate incorporating AR splice variation into our analysis of CRPC specimens over year 2 of this grant.

2d. (Revised) Classify each CRPC with respect to AR splice variation (Y1Q3)F

As discussed immediately above, this task is not complete and will continue into Year2 and Year 3 of the grant.

2e. (Revised) Classify each CRPC with respect to AR amplification (Y1Q3)F

We have not determined AR amplification in the samples collected by radiologically guided biopsy. The samples are still at Duke and need to be transferred to UCSF through a Material Transfer Agreement before this analysis will be performed. We anticipate this to occur during the second year of the study.

2f. (Revised) Classify each CRPC with respect to AR activity, androgen levels, AR splice variation, and AR copy number (Y1Q4)F

We have applied our AR signature to a total of 187 specimens – 31 biopsies from CRPC tumors for men participating in our AR signature trial. In addition, we applied the AR signature to data from 156 prostate cancer specimens from a recent paper publication. The AR signature has been applied to the 31 specimens passing quality; 14 (45%) had relatively high levels of AR activity and 17 (55%) had relatively low levels of AR activity. This distribution is similar to what we had reported earlier (Mendiratta et al JCO 2009) [2]. These classifications will be used in year 2 to identify pathways associated with low levels of detected AR activity (Task 2g).

Application of the AR signature to expression data from Taylor et al. has helped to accelerate this task and provide data in support of Task 2g. We have applied the AR signature to all samples from this dataset in order to determine the distribution of AR activity and identify specimens with low levels of AR activity. **Figure 2** demonstrates the distribution of AR activity in primary prostate cancer (green), metastatic prostate cancer (red), and prostate cancer cell lines (blue). Importantly, the distribution of the cell lines reflects the known AR activity status of the cell lines studied (LNCaP is high, other AR-null cell lines were low). For local tumors, 82 tumors (64%) had AR activity greater than 0.50 while 46 (36%) had low AR activity. Metastatic tumors had the opposite distribution with a greater number of samples with low levels of AR activity with 12 samples (67%) have levels less than 0.5 and 6 samples (33%) with activity greater than 0.50. Identification of samples with low levels of AR activity provides the opportunity to determine those pathways that may be facilitating androgen receptor independent prostate cancer growth.

Milestone #4: (Revised) Impact of AR splice variation and AR genetic amplification on classification of CRPC specimens into AR-specific states (Y1Q4)

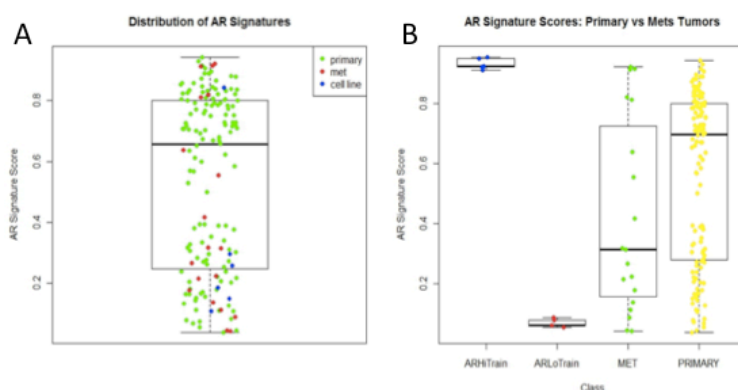


Figure 2: AR levels in Prostate Cancer Specimens. The AR expression-based signature was applied to prostate cancer specimens from Taylor et al Cancer Cell 2010. A) Distribution of all samples, B) Distribution of training samples and metastatic samples (green) separated from local prostate cancer tumors (yellow)

This aim/milestone is in progress but nearing completion. Working together, we have classified the prostate cancer metastasis based on gene expression profiles into AR activity categories and are now subdividing the AR activity 'high' category, representing the >90% of the tumors, into subcategories based in AR splice variant status with or without AR amplification status. The preliminary results indicate that the major if AR activity 'high' category also has AR amplification, ~60%. Completion of AR splice variant analysis is

pending as several distinct splice variant forms have recently been identified and will be included in the analysis.

2g. Associate additional pathways with ARIPC.
(Y1Q4)—F

The Febbo laboratory has applied an integrative model to identify pathways associated with low levels of AR activity. This work has been performed in collaboration with Dr. Terry Furey who is now at University of North Carolina, Chapel Hill. We have applied an analytic approach termed ASSESS that is an extension of Gene Set Enrichment Analysis but uses both expression and copy number variation in order to associate gene sets with a phenotype (Xiong Q et al “Integrating genetic and gene expression evidence into genome-wide association analysis of gene sets.” *Genome Res* (2012);22(2):386-97) [3]. Using this approach, we classified prostate cancer specimens based upon their detected levels of AR activity (Established in Task 2f) with a cut-off at a relatively low level of 0.15 (i.e. probability of AR activity <0.15 vs. >0.15). **Figure 3** demonstrates the top pathways implicated in this analysis. This unbiased analysis used the pathways from the Molecular Signatures Data Base at the Broad Institute (“MSigDB” [4]) which contains over 1000 gene sets annotated for their relevance to specific biological processes or pathways. We have used this database of genesets for prior analysis but this is the first application of GSAA to prostate cancer specimens and represents truly integrative analysis (both RNA and DNA data). While these results require validation and analysis (Task 2h in Year 2), they provide some compelling hypotheses. For examples, many gene sets with a significant association with low AR phenotype involve immune-related phenomenon such as immunoregulatory interactions, dendritic cell pathways (“Biocarta_DC_Pathway”, cytokines (“Biocarta_IL17_Pathway”, “Biocarta_Cytokine_Pathway”, “Biocarta_IL2_Pathway”, or inflammation “Biocarta_Inflam_Pathway”. These suggest that the immune system may be either facilitating androgen-independent growth or responding to cells that are truly AR independent. In addition, two different developmental pathways are implicated – Neuronal (“Reactome_NA_CL_Dependent_Neurotransmitter_transporters” and “Reactome_Glutamate_Neurotransmitter_Release_Cycle”) and Stem Cell (“Biocarta_Stem_Pathway”). Both neuronal and stem-like differentiation have been previously described in model systems of prostate cancer that have become less dependent on the androgen receptor and these observations help validate our approach and underscore the human relevance of these developmental adaptations. Targeting either neuronal differentiation or stem-cell pathways may provide therapeutic opportunities as there are a number of agents targeting these pathways. Finally, there are a significant number of pathways involving transporters; if validated, these may be additional targets for therapy.

While we do not see SRC, MYC, HDAC, etc implicated in this set of pathways, we have only shown those pathways meeting the most stringent statistical criteria (FDR <0.25). We will continue to analyze the 360

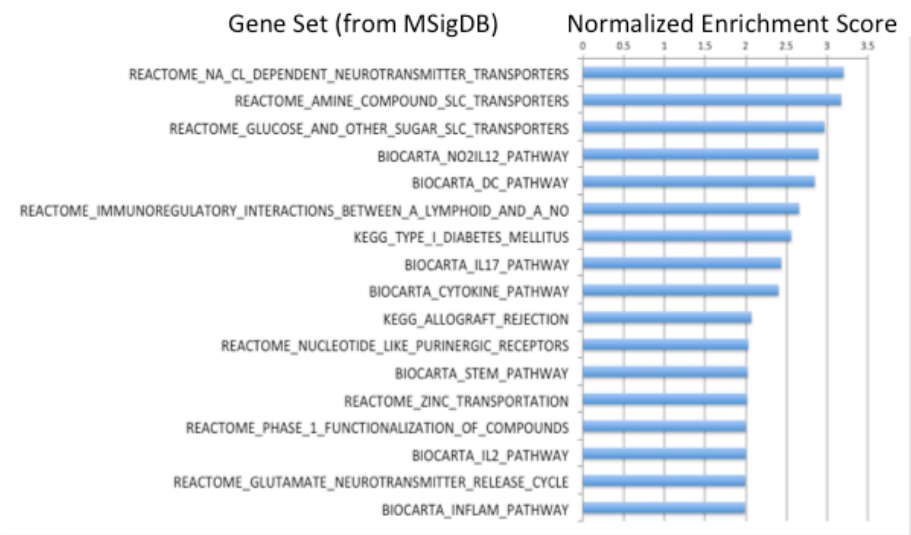


Figure 3: Pathways identified by Gene Set Association Analysis (GSAA) in samples with low levels of AR activity (AR Probability <0.15). Pathways are shown with a False Discovery Rate of <0.25.

prostate cancer specimens for AR activity and refine our analyses so as to identify those pathways with the strongest association with low AR activity in prostate cancer.

2h. Validate additional pathways with ARIPC (Y2Q4)—NF

Task has commenced, to be continued in Year 2.

Milestone #5: Identifications of additional pathways associated with ARIPC (Y2Q2)

As demonstrated above, this task has commenced, to be continued and possibly completed in Year 2.

Task 3: Analysis of scientific aim 2: To determine if targeting/inhibiting the pathway(s) associated with ARIPC will restrain prostate tumor growth.

3a.(Revised) Determine the impact of inhibiting MYC in ARIPC (Y2Q4)-N

Task has commenced, to be completed in Year 2. Preliminary data indicates that Myc expression may bypass the requirement for maintenance of AR activity.

3b. (Revised) Determine the impact of targeting HDAC family members in ARIPC (Y2Q4)—F

Task to Dr. Febbo. To be started in Year 2.

Milestone #6: (Revised) Results demonstrating the impact of MYC and HDAC inhibition on ARIPC xenografts (Y2Q4)

To be started in Year 2.

3c. Determine the impact on ARIPC growth of inhibition of candidate pathway #1 identified during Tasks 2g and 2h--(Y3Q3)NF

To be completed in Year 3.

3d. Determine the impact on ARIPC growth of inhibition of candidate pathway #2 identified during Tasks 2g and 2h--(Y3Q4) NF

To be completed in Year 3.

3e. Determine the impact on ARIPC growth of inhibition of candidate pathway #3 identified during Tasks 2g and 2h--(Y3Q4)NF

To be completed in Year 3.

Milestone #7: Results demonstrating the impact of inhibition of candidate pathways #1, #2, and #3 on ARIPC xenografts --(Y3Q4)

To be completed in Year 3.

Task 4: Analysis of scientific aim 3: To determine if simultaneously co-targeting the AR pathway and ARIPC survival pathway(s) in AR-sensitive prostate cancers will augment tumor responses and delay/prevent recurrences.

4a.(Revised) Determine the impact of co-targeting AR and the most promising pathways out of SRC, MYC, OxPhos or HDAC in castration sensitive prostate cancers. (Y2Q4)-N

This has been started by the Nelson Laboratory and details are provided in their Annual Progress Report.

4b. (Revised) Determine the impact of co-targeting the second most promising pathways out of SRC, MYC, OxPhos or HDAC in castration sensitive prostate cancers.- (Y2Q4)N

Studies to be completed by Y2Q4

Milestone #8:(Revised) Results demonstrating the impact of cotargeting AR and either MYC or HDAC inhibition on prostate cancer xenografts. (Y2Q4).

Studies initiated (see above). To be completed by Y2Q4.

4c. Determine the impact on hormone naïve prostate cancer xenograft growth of co-targeting candidate pathway #1 and AR (Y3Q3) NF

Studies to be completed in Y3Q3.

4d. Determine the impact on hormone naïve prostate cancer xenograft growth of co-targeting candidate pathway #2 and AR (Y3Q4)NF

Studies to be completed in Y3Q4.

4e. Determine the impact on hormone naïve prostate cancer xenograft growth of co-targeting candidate pathway #3 and AR (Y3Q4) NF

Studies to be completed in Y3Q4.

Milestone #9: Results demonstrating the impact of co-targeting AR and candidate pathway #1, #2, or #3 on prostate cancer Xenografts

Studies to be completed in Y3Q4.

Task 5: Reporting of protocol processes (To begin year 2).

5a. Review and summarize pathways specifically associated with ARIPC (Y2Q2)

Studies to be completed in Y2Q2.

Milestone #10: Abstract submission to AARC annual meeting reporting pathways associated with ARIPC (Y2Q2)

Studies/abstract to be completed in Y2Q2.

5b. Prepare manuscript reporting identification and validation of pathways specifically associated with AIRPC (Y2Q3)

Studies/manuscript to be completed in Y2Q3.

Milestone #11: Submit abstract/manuscript reporting identification and validation of pathways associated with AIRPC (Y2Q3)

Studies/abstract to be completed in Y2Q3.

5c. Prepare manuscript reporting the impact of inhibiting SRC in castration sensitive and ARIPC prostate cancer xenografts (Y3Q2)

Studies to be completed in Y3Q2.

Milestone #12: Submit abstract/manuscript reporting impact of SRC inhibition in castration sensitive and ARIPC xenografts (Y3Q2)

Studies to be completed in Y3Q2.

5d. Prepare manuscript reporting the impact of inhibiting oxidative phosphorylation in hormone naïve and ARIPC xenografts (Y3Q2)

Studies to be completed in Y3Q2.

Milestone #13: Submit manuscript reporting impact of oxidative phosphorylation inhibition in castration sensitive and ARIPC xenografts (Y3Q2)

Studies to be completed in Y3Q2.

5e. Prepare manuscript reporting on the impact of inhibiting candidate pathways #1, #2, and/or #3 in hormone sensitive and ARIPC xenografts (Y3Q4)

Studies to be completed in Y3Q4.

Milestone #14: Submit abstract/manuscript reporting on the impact of inhibiting candidate pathways #1, #2, and/or #3 in hormone sensitive and ARIPC xenografts (Y3Q4)

Studies to be completed in Y3Q4.

Key Research Accomplishments

- We have completed the laser capture microdissection and q/c of attendant RNA from 54 radiologically-guided biopsies from castration resistant prostate cancers. (Total with the Nelson Lab = 204)
- We have completed transcript profiling (including AR expression) from 31 prostate cancer metastasis (those with suitable quality RNA).
- We have obtained a high-quality dataset from a recent publication including RNA microarray and DNA microarray data for 156 prostate cancer tumors to complement the samples we are processing as part of our Synergistic Idea Development Award.
- We have initiated the network analyses integrating transcript and copy number variation to define molecular pathways operative in CRPC.
- We have implicated developmental pathways involved in neuronal and stem-cell differentiation with prostate cancers having low AR-activity.

Reportable Outcomes

We have not published findings from this project during the first year of this report.

Conclusion

We have largely completed the proposed year 1 tasks and have made outstanding progress on our proposed aims. While we elected not to pursue AR splice variant identification during the first year, we have applied our AR signature of activity to more than our goal of 150 prostate tumors and we have performed integrative analysis to identify pathways associated with androgen receptor independent prostate cancer tumors. We will continue to use data from the CRPC tumors to identify the most important pathways in AR-independent CRPC tumors and validate and target these tumors during years 2 and 3 of this grant.

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